

# THE ACTION OF ADRENALIN IN NEUROTICS

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(RECEIVED 26TH FEBRUARY, 1942)

## Literature

SINCE Cannon (1915) demonstrated that emotional stress is associated with an increased and prolonged secretion of adrenalin, attention has been directed to the relationship of the effects of adrenalin and the symptoms of anxiety. Maranon (1924), giving subcutaneous injections of the drug, observed effects varying from a vague apprehension to severe emotional disturbance and concluded that an exaggerated response is shown by anxiety neurotics. He demonstrated that emotion is not directly determined by the physical phenomena and that intense physical reaction can occur without emotional response. The emotion may not necessarily be that of fear, and a case experiencing great joy was described.

Richter (1940) suggested that the emotional response may be due to the physical effects of the injection and claimed to have eliminated this by the introduction of adrenalin electrically through the skin. By this method he confirmed Maranon's findings, agreed that emotions other than fear may occur, and described an asthmatic who experienced a sensation of confidence after injection. He concluded that conæsthetic impulses arising from visceral disturbances excite an emotionally charged cortical pattern so that each tends to increase the degree of excitation of the other.

Lindemann and Finesinger (1938) injected mecholyl and adrenalin intramuscularly into a group of neurotics. They objected to the intravenous route on the grounds of the rapid rise and fall of blood pressure which occurs and preferred the slower intramuscular route as it gave time for more prolonged observation. They found four groups: (1) specific response to adrenalin, (2) specific response to mecholyl, (3) reaction to both drugs, (4) no response to either. In the adrenalin-sensitive group the anxiety attacks were found to be unrelated to specific situations or mental content and were thought to coincide with Freud's "actual neurosis." The mecholyl-sensitive group were those with definite phobias and fears. The mixed group had a history of autonomic instability and hypochondriasis and the last group indicated more profound personality disorders. The writers recorded that in the adrenalin attack there is a surrender to anxiety, associated with diminished speech production, while in the mecholyl attack there is an active attitude directed to the environment, with increased speech production, associated with phobic states.

To return to the physiological aspect: the question arises as to what constitutes a normal response in terms of rise in blood pressure and pulse rate to the action of adrenalin. Clark (1940) states that in response to 1 c.c. adrenalin injected subcutaneously, the blood pressure may rise 75 mm. Hg in the sympathicotonic, 20 mm. in the normal, and may fall 10 mm. to rise 10 mm. in the vagotonic individual. It is impracticable to discuss adequately here the literature concerning this classification. Kuntz (1934), reviewing the wealth of papers which has accumulated since Eppinger and Hess (1909) postulated vagotonic and sympathicotonic types, quotes Petsen and Thorling's criticisms, chief of which are that symptom-complexes of vagotonia, e.g. asthma, may have sympathetic symptoms and may over-react to sympathetic stimuli, and similar observations can be made about sympathicotonia, e.g. hyperthyroidism.

Misch (1935), in discussing the genesis of the syndrome of neurotic anxiety, considers the acute major attack to be a sympathetic phenomenon followed by a para-sympathetic swing, and in the chronic form to exhibit a mixture of sympathetic and para-sympathetic symptoms. In addition, he refers to Oppenheim (1909) as having postulated a congenital weakness of the vasomotor visceral apparatus and saying that anxiety has not only a somatic but also a psychical origin, resting on an unusual reaction of the vegetative nervous system to ideas and sense impressions. Evidence of this neuro-circulatory inadequacy has been shown by McFarland and Huddleson (1936) by use of the Schneider Index (an index of the changes in pulse rate and blood pressure when the patient changes from lying to standing and has an undue response to an exercise tolerance test). The index is markedly raised in anxiety states as compared with other forms of psychopathy and with normal individuals.

On this evidence it remains open whether, in cases of anxiety neurosis, (1) sensitivity is expressed as an over-reaction physiologically to the drug, (2) sensitivity is an over-reaction mentally to visceral sensations that are no more marked than in the normal individual, or (3) both mechanisms are playing a part.

### Clinical Material

Thirty-five patients, comprising three main groups, (1) anxious, (2) anxiety + other features, (3) not anxious, were investigated. The first described the visceral sensations accompanying fear in a severe form and arising from experiences in the Battle of France, air-raids over this country, or the rigours of service life. It appeared that their physiological equilibrium was unduly unstable and that they were upset by stimuli that did not have such a severe effect on the majority of their comrades. They were usually of the asthenic physique and showed such indications of instability as a tendency to be easily intimidated, worry over trifles, flush easily, and lack self-confidence.

The second group, in addition to anxiety, present other important features, such as hysterical amnesia, depression, or symptoms referable to a head injury of some severity. The last group was a miscellaneous collection not obviously

presenting somatic anxiety and consisted of patients suffering from gastric neuroses, stammer, and organic syndromes.

Of the fifteen patients in the anxious group, the symptoms of twelve had been aggravated by enemy action and of the other three by the conditions of service life. In six of these patients a near relative had shown definite evidence of mental disorder. Thirteen showed previous evidence of neurotic traits and all exhibited some such personality defect as shyness, timidity, excessive worrying, and undue sensitivity.

Of the eleven patients in the second mixed group, the symptoms of seven had been precipitated by bombing and of the remainder by service life. Eight had evidence of familial psychopathy, eight showed previous neurotic traits, and in all there was a defect of personality.

In the third group of nine non-anxious subjects, four had a positive family history of mental instability, five had previous neurotic traits, and seven had minor personality defects.

### Experimental Method

The effects upon the pulse and blood pressure and the symptoms noticed by each patient after an intramuscular injection of adrenalin have been recorded. The intramuscular route was chosen because of the violent symptoms produced by the intravenous method.

Before the administration of adrenalin, saline was given intramuscularly, to accustom the patient to an injection, and was repeated if there was an undue response. In spite of the saline injections, it was impossible to prevent the subjects realizing that a drug had been given, and they complained of the local pain produced. Before an estimate of the effect produced by adrenalin could reasonably be made, it was essential to obtain a fairly stable pulse rate and blood pressure. This proved unexpectedly difficult, and in one particularly apprehensive subject, his nervousness, tremor (which was increased by the tightening of the sphygmomanometer band), palpitations, and præcordial pain disappeared only after 50 minutes; during this time his systolic blood pressure fell 35 mm. Hg. The difficulty generally experienced, however, was in waiting for a diminution in the range of oscillations rather than in a steady fall of the readings. In one patient, after saline the systolic blood pressure oscillated from 150 to 115 mm. Another patient fainted while his blood pressure fell to 80 mm. and his pulse to 60 per minute after an injection of saline. The systolic blood pressure was considered to be "resting" when it did not vary more than 10 mm. during a period of 5 minutes before injection. The highest pulse rate or blood pressure reading reached after injection, less the highest figure in the "resting" period, constituted the presumed response to adrenalin. The readings were continued until the blood pressure was obviously going to fall consistently—a period lasting up to half an hour.

In order to reassure patients, they were examined while sitting comfortably in a chair. Two series of adrenalin doses were given: amounts of the order of 1 c.c., to make a comparison with Clark's figures, and smaller quantities

because it was thought that with such an amount undue sensitivity would be more apparent.

### Results

None of my patients, in response to adrenalin, produced effects outside the limits given by Clark's Pharmacology, as quoted above. In the following observations a rise in blood pressure greater than 20 mm. Hg is considered to be a brisk response. If it is justifiable to take Clark's figure of 20 mm. as a normal response to 1 c.c. adrenalin injected intramuscularly, it is certainly reasonable with smaller quantities. Since no similar arbitrary figure for pulse rate has been encountered in the literature and as only two patients in the whole series gave a rise in pulse rate greater than 30 beats per minute, this factor does not warrant further consideration.

In view of possible criticism of the findings obtained from sitting patients, eight subjects were examined lying down (Table II). Of nine sitting patients, five showed a significant rise in blood pressure, and of the eight lying patients, the blood pressure rose markedly in three. Although the number is small, there is nothing in the findings to suggest that posture affects the changes in blood pressure resulting from intramuscular injections of adrenalin.

As already mentioned, patients were divided according to dose into two groups: small (0.5 to 0.75 c.c.) and large (0.8 to 1.2 c.c.). Table I shows that eight out of twenty-four patients had a rise in systolic blood pressure greater than 20 mm. Hg, as had eight out of sixteen subjects receiving the larger dose (Table II). One expects such a finding, but a glance at the tables shows that the extent of rise in blood pressure is not proportionate to the dose of adrenalin. The seven cases marked by asterisks in Tables I and II are common to both groups. Of the four patients whose blood pressure did not rise significantly in response to a small dose of adrenalin, only one gave an undue rise of blood pressure with the larger dose. Although there is a tendency for larger intramuscular injections of adrenalin to produce greater rises in blood pressure, the rise is by no means directly proportionate to the dose.

As far as the question of whether anxious patients show an undue rise of blood pressure is concerned, of those receiving a small dose, five out of eleven in Group I, one out of six in Group II, and two out of seven in Group III gave significant responses (Table I). In the larger dose-group (Table II), the comparable figures were: Group I, four out of seven; Group II, three out of seven; Group III, one out of three. Using the small dose, a greater number of patients of the anxious class appear to be unduly sensitive, but the figures are too small to meet statistical requirements.

It may be thought that the differences between the effects of the various injections of adrenalin are due to variations in the rate of absorption. The following observations indicate that other factors play a very important part in determining any individual response. Case I (1) in Table III, whose systolic blood pressure fell in response to an injection of saline, after experience of adrenalin responded by a rise in blood pressure to saline; thus indicating a

TABLE I.—SMALL DOSE (0.5 TO 0.75 C.C. ADRENALIN) †

TABLE II.—LARGE DOSE (0.8 TO 1.2 C.C. ADRENALIN) ‡

CASE NO.	DOSE	RISE B.P.	RISE P.R.	CASE NO.	DOSE	RISE B.P.	RISE P.R.
I (1)*	0.5	40	8	SITTING			
(2)*	0.5	10	20	I (1)*	0.8	40	4
(3)*	0.5	30	30	(2)*	1.0	5	-4
(4)	0.5	20	8	(3)*	1.0	45	-8
(5)	0.6	25	12	II (1)	0.9	15	24
(6)	0.6	25	8	(2)*	1.0	30	12
(7)	0.6	15	16	(3)*	1.0	15	4
(8)	0.6	15	-8	(4)	1.0	35	20
(9)	0.65	20	4	(5)*	1.2	35	12
(10)	0.7	20	4	III (1)*	1.0	20	4
(11)	0.75	25	24	(2)	1.0	15	20
II (1)* (a)	0.5	-10 to +10	-8 to +8	LYING			
(b)	0.6	25	4	I (1)	0.8	20	12
(2)*	0.5	10	8	(2)	0.85	20	36
(3)*	0.6	15	16	(3)	0.9	25	12
(4)	0.65	20	4	(4)	0.9	25	12
(5)	0.7	10	8	II (1)	0.85	20	16
(6)	0.7	15	0	(2)	1.0	20	20
III (1)*	0.5	15	4	(3)	1.0	20	16
(2)	0.6	10	20	III (1)	0.9	30	20
(3)	0.65	5	8				
(4)	0.65	15	4				
(5)	0.7	20	4				
(6)	0.7	35	12				
(7)	0.75	25	24				

\* Cases common to both groups.

† Dose estimated on basis of 0.1 c.c. adrenalin per kilogram body weight.

‡ Dose estimated on basis of 0.1 c.c. adrenalin per 0.2 sq. metres surface area.

TABLE III

CASE NO.	EXPT.	RESTING PERIOD	DRUG	RISE B.P.	RISE P.R.
I (1)	(a)	10 mins.	Saline.	-10	4
		10 "	0.6 c.c. adrenalin.	20	4
	(a)	23 "	Saline.	25	-8
I (2)	(b)	28 "	"	15	0
	(a)	14 "	0.6 c.c. adrenalin.	25	20
	(b)	38 "	0.6 c.c. "	40	16
	(c)	36 "	0.6 c.c. "	55	32
	(d)	55 "	0.1 mg. acetyl-choline.	-10	-6
	(e)	34 "	0.1 mg. "	+5	0
		25 "	0.6 c.c. adrenalin.	20	-4
I (3)	(f)	42 "	0.6 c.c. "	35	4
	(a)	43 "	Saline.	-5	0
		11 "	"	10	12
	(b)	11 "	"	-20	4
		43 "	"	10	8
	(c)	40 "	0.1 mg. acetyl-choline.	-5	16
	(d)	42 "	0.5 c.c. adrenalin.	20	8
	(e)	59 "	Unexpected pistol shot.	15	0
		11 "	" " "	20 to -10	8
		8 "	" " "	0	0
	6 "	0.5 c.c. adrenalin.	-10	0	
	8 "	Unexpected pistol shot.	0	0	
	4 "	" " "	-15 to +15	4 to -4	
II (1)	(a)	40 "	0.6 c.c. adrenalin.	5	-4
		22 "	0.1 mg. acetyl-choline.	-10	4
		23 "	Psychological stimulus.	35	24

factor of "expectancy." Case I (2) in the same table illustrates the effect of increasing apprehension of the test and a fear of the visceral sensations produced. The blood pressure and "resting-time" increased with each successive experiment; the responses to saline have been omitted as no striking features were shown. This "conditioning" effect was temporarily removed by substituting acetyl-choline (also painful) for adrenalin, although the subject was able to detect the difference between the subjective effects of the two drugs. The findings suggest an increasing response to the visceral sensations produced rather than a reaction to a local painful injection. Case I (3) illustrates that a subject's systolic blood pressure may fall further in response to saline than to acetyl-choline, though his response to adrenalin remains normal; when frightened by the unexpected firing of a pistol, his blood pressure fell in response to adrenalin but subsequently oscillated violently when another shot was fired. On another occasion, this subject's blood pressure rose 45 mm. and his pulse rate 24 at reference to such painful topics as knives, suicide, and Southampton air raids, and also on serially subtracting seven from 100. Case II (1), who had shown a normal response to a small dose and a brisk response to a larger dose of adrenalin, was practically unmoved by 0.6 c.c. adrenalin after his discharge from the Army. A reference to this topic, however, 45 minutes later, and in spite of an intermediate injection of acetyl-choline, gave a rise in blood pressure of 35 mm. Hg and an increase of 24 beats a minute in pulse rate.

Such results as these show the impracticability of the concepts "sympathicotonia" and "vagotonia." They illustrate the importance of emotional factors and previous experience of the drug in determining blood pressure responses.

### Subjective Findings

Table IV gives the frequency with which various symptoms and signs occurred in each clinical group, under the varying conditions of the onset of experimental situations, receiving injections of saline and adrenalin. As the results vary when the test is repeated, only the responses to the first experiments and injections of saline and adrenalin respectively are given. Since patients were encouraged to give their descriptions spontaneously, accounts depend on the form of neurosis, intelligence, and co-operation of the subject. Such physical signs as tremor, changes of colour, holding the breath, and sweating (central, i.e. sweating of palms) have been included only if they were obvious or were complained of by the patient. In order to discover whether any correlation exists between symptoms and rise in blood pressure, the patients have been divided into two groups: those in whom the systolic blood pressure rose more than 20 mm. Hg and those who did not exhibit such a change. The incidence of symptoms was greater in the anxious subjects in response to the situation, saline, and especially adrenalin in the group which did not show a significant rise of blood pressure.

It is of interest to note that one patient burst into tears after the injection

of adrenalin because the resultant sensations, tremor, and "stomach turning over" reminded him of an occasion when his Commanding Officer accused him of malingering. One patient distinguished between the symptoms produced and those of an anxiety attack by mentioning the absence of the "hot feeling," and another made the distinction by the absence of the "sinking sensation in the stomach." This latter described the sensations after an injection of acetyl-choline followed by adrenalin as "like an attack—he had a sensation of fear which he was holding in." In five of the lying patients, fifteen minutes after adrenalin, when they had passed their maximum response, further symptoms were brought out by asking the patient to stand up, and in four of them an Exercise Tolerance Test increased the symptoms present or produced further ones. No persistent effect was observed upon blood pressure. Symptoms so resulting were not included in the above tables.

TABLE IV

	GROUP I (8 PATIENTS)			GROUP II (9 PATIENTS)			GROUP III (6 PATIENTS)		
	SITN.	SAL.	ADREN.	SITN.	SAL.	ADREN.	SITN.	SAL.	ADREN.
<i>Rise of Systolic B.P. less than 20 mm. Hg:</i>									
Total No. symptoms . .	19	13	34	20	9	22	7	5	16
Average No. per patient	2.4	1.6	4.2	2.2	1.0	2.4	0.8	0.8	2.7
<i>Rise of Systolic B.P. more than 20 mm. Hg:</i>									
Total No. Symptoms	15	4	26	9	2	11	9	7	16
Average No. per patient	2.1	0.5	3.7	4.5	1.0	5.5	3.0	2.3	5.3

Nine patients had an unusually low blood pressure which oscillated around a figure between 90 and 110 mm. Hg. Seven of them had pure anxiety states in Group I and in three of these adrenalin produced a significant rise of blood pressure. The other two were in Group II and one exhibited an undue lability of blood pressure in response to a large dose of adrenalin.

These findings indicate that anxiety neurotics show a sensitivity to intramuscular injections of adrenalin which is expressed in an increased number of symptoms referable to all physiological systems. Other factors, common in anxiety neurotics, not directly related to each other or to symptomatology, are the undue lability of blood pressure and an unusually low resting blood pressure. Such findings may occur in any psychoneurotic individual but occur more frequently in the constitutionally anxious types.

### Summary and Conclusions

1. In a review of the literature the views of various authors upon the sensitivity of patients with anxiety state to adrenalin have been given. The observed sensitivity to adrenalin is generally regarded as being a common feature of anxiety neurosis.

2. Thirty-five neurotic service patients, forming three clinical sub-groups, were investigated. Evidence of familial psychopathy, previous neurotic traits, and inadequacies of personality were a marked feature in their previous records.

3. The difficulty of obtaining "resting" pulse rate and blood pressure readings and of deciding what constitutes an abnormal response is demonstrated.

4. With small intramuscular doses of adrenalin, a significant rise of blood pressure was found more frequently in patients with anxiety states than in those of other clinical sub-groups. The response varied from patient to patient and from time to time in the same subject. It did not vary proportionately with the dose of adrenalin and depended rather on the mental state of the patient, his previous experience of the drug, and his reaction to the visceral sensations produced.

5. In the absence of a rise in blood pressure, the appearance of symptoms is more frequent after adrenalin injections in anxiety states than in other groups. Sensitivity in subjective experience is not related to the labile blood pressure and the low blood pressure which are common features of this clinical group.

#### Acknowledgments

My thanks are due to Dr. L. Minski, Medical Superintendent of the Emergency Hospital, for permission to use the clinical material, and to Dr. Eliot Slater, Clinical Director, without whose kindly advice this work would not have been completed.

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